REMARKS

This Response is to the Office Action, dated March 24, 2010 ("Office Action"). It is respectfully submitted that the application is in condition for allowance. No new matter has been added. Allowance and reconsideration of the application in view of the ensuing remarks are respectfully requested.

Claims 15-19 are rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter for reasons of record. Particularly, the Examiner asserts that the intended use of the cells would include cells in humans that would be an integral and inseparable part of the human. Further, the Examiner cites to MPEP §2105 and asserts that since the cells "embrace the human that carries them," they are non-statutory subject matter. Applicants respectfully traverse this rejection.

A nonnaturally occurring manufacture or composition of matter is patentable subject matter. MPEP §2105 (citing Diamond v. Chakrabarty, 447 U.S. 303 (1980)). With respect to inventions involving a human being, it is only when "the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being" that a rejection under 35 U.S.C. §101 must be made. MPEP §2105 (emphasis added).

Applicants respectfully submit that the Examiner has misapplied §101 and the prohibition against patenting human beings. It is only when the invention encompasses the human being that it is nonstatutory subject matter. However, when the invention is encompassed by the human being, it can be patentable subject matter. Otherwise, by the Examiner's logic, countless numbers of inventions would be nonstatutory subject matter. For example, a chemical composition administered into a human being that integrates into the cells would be nonstatutory subject matter by the Examiner's logic. A dental implant that replaces a human being's tooth would be nonstatutory subject matter by the Examiner's logic. Clearly, these items are patentable subject matter under §101.

Claims 15-19 are directed to endothelial cells, produced by a method wherein the endothelial cells comprise a retrovirus expressing PTN. These cells are nonnaturally occurring cells. These cells do not encompass a human being. Simply stated, the broadest reasonable interpretation of these claims does not encompass a human being because a human being is more than just endothelial cells. Accordingly, these cells are patentable subject matter under §101. In

light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1 and 11 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* for reasons of record. The Examiner asserts that one of ordinary skill in the art could, upon reading Havemann *et al.*, Souttou *et al.*, and Powers *et al*, reasonably conclude that pleiotrophin (PTN) may be used for inducing differentiation of monocytic cells to endothelial cells.

In response to Applicants' previous arguments, the Examiner responds with the following. The Examiner asserts that Havemann *et al.* discloses a small list of growth factors to be used when differentiating monocytic cells to endothelial cells and asserts that one "need only provide PTN to the monocytes and observe the corresponding effect." The Examiner argues that VEGF and FGF are species within the same genus that embraces PTN and thus, one of ordinary skill in the art would reasonably conclude that VEGF and FGF are examples of and refer to other angiogenic growth factors. The Examiner further argues that PTN was known to be involved in growth and differentiation and cites Deuel *et al.* and Pufe *et al.* The Examiner additionally argues that Havemann *et al.* discloses "the transfection of mononuclear cells with a nucleic acid construct for gene therapy, wherein the construct comprises an effector gene [0023], the effector gene being a growth factor [0047], the growth factor including PTN [0074]." The Examiner asserts that only knowledge within the level of ordinary skill at the time the claimed invention was made was taken into account and no impermissible hindsight was exercised. The Examiner finally maintains that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Applicants respectfully traverse this rejection.

In determining whether a claimed invention is *prima facie* obvious, the Examiner must not use impermissible hindsight; rather "the content of the prior art must be determined at the time the invention is made." MPEP §2141.01(III). Additionally, "in determining the differences between the prior art and the claims, the question…is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP §2141.02(I), emphasis in original, (citing Stratoflex, Inc., v. Aeroquip Corp., 713 F.2d 1530 (Fed. Cir. 1983). Further, "distilling an invention down to the 'gist' or 'thrust' of

an invention disregards the requirement of analyzing the subject matter 'as a whole.'" Moreover, "treating the advantage as the invention disregards statutory requirement that the invention be viewed 'as a whole.'" MPEP §2141.02(II), citing W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983) and Jones v. Hardy, 727 F.2d 1524, 1530 (Fed Cir. 1984). Additionally, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP §2143.01 (citing KSR International Co. v. Telefex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007)). As such, a "reasonable expectation of success is required." MPEP §2143.02. Furthermore, a patent cannot be relied upon to the extent that the scope of its disclosure does not reasonably suggest those aspects relied upon in the rejection. MPEP §2123 (citing Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)).

The combination of Havemann *et al.* with Soutou *et al.* and Powers *et al.* is improper

First, Applicants respectfully remind the Examiner that Applicants are not merely attacking references individually; Applicants are disagreeing with the Examiner's erroneous interpretation of the references. The concept that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references" would be based on a premise that each individual reference indeed teaches what is alleged by the Examiner. However, when the Examiner has erroneously interpreted a prior art reference, and the erroneous interpretation is providing the basis and/or rationale for obviousness, then by attacking the Examiner's erroneous interpretation, Applicants are also showing that the combination of the prior art would not be proper and thus, would not render the claimed invention obvious.

Applicants' claimed invention is directed to a method of transdifferentiating a monocytic cell into an endothelial cell by transducing the monocytic cell with a retrovirus expressing PTN to thus artificially increase the expression of PTN and induce the transdifferentiation of the monocytic cell into the endothelial cell; and an endothelial cell produced by this method. The Examiner must not lose sight of whether this invention as a whole, e.g., the monocytic cell is transduced with the retrovirus expressing PTN to induce transdifferentiation of the monocytic

cell into the endothelial cell, would be obvious in light of the combination of Havemann *et al.* with Souttou *et al.* and Powers *et al.*

Applicants respectfully submit that the Examiner has not analyzed the subject matter as a whole. Rather, the Examiner has looked at whether the differences between the claimed invention and the prior art would have been obvious. This is evident in the Examiner's rejections as discussed below.

Havemann et al. does not teach the use of PTN to differentiate monocytic cells into endothelial cells

The Examiner has looked at the difference between Havemann *et al.*'s teaching regarding a method of culturing mononuclear cells under differentiation conditions of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells and Applicants' claimed method of using the transduction of a retrovirus expressing PTN into the monocytic cell to transdifferentiate the monocytic cell into an endothelial cell.

First, the Examiner has erred by focusing on this difference rather than focusing on the invention as a whole.

Second, Applicants respectfully submit that the Examiner continues to misinterpret the teachings in Havemann *et al.* Havemann *et al.* describes methods of culturing mononuclear cells under differentiation conditions of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells. One of ordinary skill in the art would appreciate that these differentiation conditions are different from using one growth factor, particularly PTN, to induce differentiation. (See Declaration of Rama Natarajan, Ph.D., ¶14.) Applicants also remind the Examiner that the actual examples in Havemann *et al.* do not include PTN in its culture media for differentiation. Thus, a general disclosure of culturing cells under differentiation conditions does not equate to a disclosure that PTN can be used to transdifferentiate monocytic cells into endothelial cells. (See Natarajan Declaration ¶14.) As such, Havemann *et al.* does not reasonably teach the use of PTN for differentiating monocytic cells into endothelial cells.

Havemann et al.'s disclosure of the use of a viral vector and Souttou et al.'s disclosure of PTN being an angiogenic factor do not lead one of ordinary skill in the art to combine the references to transfect a monocytic cell with a viral vector expressing PTN

The Examiner then cites to Havemann *et al.*'s disclosure regarding the use of a viral vector to transfect the cells and overlooks the fact that the Havemann *et al.*'s disclosure of this embodiment is in the context of trying to have the endothelial cell express a biologically active protein so that the protein may effect a therapy. There is no disclosure or suggestion that the cells are transfected with a biologically active protein to transdifferentiate the cell into an endothelial cell. As evidenced by Natarajan Declaration ¶15, one of ordinary skill in the art would not be led by the teachings of Havemann *et al.* to transfect a monocytic cell with a retrovirus expressing a biologically active protein to transdifferentiate the monocytic cell into an endothelial cell. As such, one of ordinary skill in the art would not look to Souttou *et al.*'s disclosure of PTN being an angiogenic factor. Even with the disclosure by Souttou *et al.*, one of ordinary skill in the art would not be led to contemplate the use of PTN in a viral vector to effect transdifferentiation of a monocytic cell into an endothelial cell. (See Natarajan Declaration ¶¶15-16.) Further, without a reasonable suggestion of using PTN to induce differentiation of monocytic cells, it would not have been obvious to transduce a monocytic cell with a retrovirus expressing PTN to induce differentiation.

The Examiner also misapplied the disclosure by Deuel *et al.* and Pufe *et al.* While Deuel *et al.* notes that PTN is involved in differentiation of glial progenitor cells, Deuel *et al.* does not teach PTN as being involved in differentiation of monocytes. Deuel *et al.* suggest that PTN is an angiogenic factor that promotes tumor angiogenesis. Pufe *et al.* does not teach that PTN is involved in differentiation. Pufe *et al.* suggests that PTN promotes replication of monocytes. (See Natarajan Declaration ¶17.) Applicants also note that paragraph [0074] of Havemann *et al.* (cited by the Examiner) is in the context of growth factors that might be suitable for inclusion in the culture media and not directed to the growth factor that is encoded by the effector gene.

The Examiner's further citation to Powers *et al.*, for its alleged teaching that PTN has autocrine and paracrine stimulatory activities in cells expressing both PTN and PTN receptor, neither rectifies the inappropriate combination of Havemann *et al.* with Souttou *et al.*, nor adds to the rationale of how the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* can render the claimed invention obvious. Powers *et al.* discloses that anaplastic lymphoma kinase

can function as a PTN receptor. Powers *et al.* makes no recognition of PTN as being useful for differentiation, let alone for differentiation of a monocyte into an endothelial cell. Accordingly, there is no motivation to combine the Havemann *et al.* and Souttou *et al.* teachings with Powers *et al.*

The Examiner, with erroneous assumptions, is cherry picking particular disclosures using impermissible hindsight and combining them in a way that does not reasonably flow from the combined teaching of Havemann *et al.* and Souttou *et al.* Applicants understand each of the Examiner's allegations and assumptions. However, the Examiner's allegations and rationale for the rejection each rest on a faulty premise.

Thus, the combination of the prior art as a whole would not render it obvious to express PTN in a monocytic cell. There is simply no suggestion by the prior art of record to one of ordinary skill in the art, even taking into account the inferences and creative steps that one of ordinary skill would have employed, to transduce a monocytic cell with PTN in order to effect transdifferentiation of the monocytic cell into an endothelial cell.

The results would not have been predictable and
there would not have been a reasonable expectation of success

Applicants maintain that the even if the references can be combined, which Applicants do not concede would be appropriate, the mere fact that they can be combined does not render the combination obvious because the results would not have been predictable to one of ordinary skill in the art and there would not be a "reasonable expectation of success" by one of ordinary skill in the art. Indeed, the Examiner still has not shown that one of ordinary skill in the art would find that a monocytic cell (as opposed to an endothelial cell) transduced with a retrovirus expressing PTN would predictably transdifferentiate the monocytic cell into an endothelial cell. As discussed above, Havemann *et al.* made no indication of which of the "one or more of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells" is responsible for differentiation of the mononuclear cells into endothelial-like cells. In its examples, only VEGF and bFGF were added in the culture media. (Havemann *et al.*, paragraphs 0247-0249.) Souttou *et al.* and Powers *et al.* do not suggest PTN as a differentiation agent. Thus, it would not be reasonably predictable to one of ordinary skill in the art that PTN alone can induce

transdifferentiation of a monocytic cell into an endothelial cell when transduced into the cell. (See Natarajan declaration ¶19.)

The invention as a whole – transdifferentiation of monocytic cells into endothelial cells by transducing a retrovirus expressing PTN – would not be obvious in view of the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 3 is rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.*, as applied to claims 1 and 11 *supra*, and in further view of Kume *et al.* The Examiner conceded that neither Havemann *et al.*, Souttou *et al.* nor Powers *et al.* teach the retrovirus expression vector to be a bicistronic retrovirus and the Examiner contended that Kume *et al.* taught the use of bicistronic retroviral vectors containing a marker gene (*e.g.*, green fluorescent protein). Thus, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to substitute the retroviral expression vector by Havemann *et al.* with a bicistronic retroviral expression as taught by Kume *et al.* Applicants respectfully traverse this rejection.

Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.* and Kume *et al.* would not render claim 3 obvious. For all the reasons discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 1 obvious because, among other things, (1) one of ordinary skill in the art would not interpret Havemann *et al.* in the manner interpreted by the Examiner, (2) one of ordinary skill in the art would not combine these teachings, and (3) there is no predictability or reasonable expectation of success for the transduced monocytic cell to transdifferentiate into an endothelial cell based on the combination. Since claim 3 depends from claim 1, it would similarly not be obvious as the determination of obviousness of the claim also takes into account, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same reasonable expectation of success. Since there is no predictability and no reasonable expectation of success from the combination of the Havemann *et al.*, Souttou *et al.* and Powers *et al.* there will not be any predictability or reasonable expectation of success for the combination of Havemann *et al.* Souttou *et al.*, Powers *et al.* and Kume *et al.*; although Applicants do not concede that it is proper to combine Kume *et*

al. with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.* and Kume *et al.*, as applied to claims 1, 3, and 11 *supra*, and in further view of Pufe *et al.*, Howett *et al.* and Eslami *et al.* The Examiner conceded that neither Havemann *et al.*, Souttou *et al.*, Powers *et al.*, nor Kume *et al.* teach the monocytes to be THP-1 monocytes. However, the Examiner contended that THP-1 cells are taught by Pufe *et al.* as being responsive to PTN stimulation; by Howett *et al.* as being useful for implantation; and by Eslami *et al.* as being capable of binding to injured human vein grafts. The Examiner concluded that it would have been obvious to one of ordinary skill in the art to substitute a first mononuclear/monocytic cell as taught by Havemann *et al.* with a second monocytic cell (specifically, THP-1) as taught by Pufe *et al.* Applicants respectfully traverse this rejection.

Applicants again suspect and submit that Kume *et al.* was erroneously applied to the rejection of claim 4. The Examiner has applied Kume *et al.* to reject claim 3; however, claim 4 does not depend from claim 3. As such, Kume *et al.* does not appear to be applicable to claim 4. Applicants again request clarification regarding Kume *et al.* Nonetheless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* would not render claim 4 obvious. As discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 1 obvious because, among other things, (1) one of ordinary skill in the art would not interpret Havemann *et al.* in the manner interpreted by the Examiner, (2) one of ordinary skill in the art would not combine these teachings, and (3) there is no predictability or reasonable expectation of success for the transduced monocytic cell to transdifferentiate into an endothelial cell based on the combination. Since claim 4 depends from claim 1, it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same reasonable expectation of success. Since there is no predictability and no reasonable expectation of success from the combination of Havemann *et al.*, Souttou *et al.*, and Powers *et al.*, there will not be any predictability or reasonable expectation of success for the combination of Havemann *et al.* Souttou *et al.* Powers *et al.*, Kume

et al., Pufe *et al.*, Howett *et al.* and Eslami *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* as applied to Claims 1, 3-4 and 11 *supra*, and in further view of Kawamoto *et al.* for reasons of record. Particularly, the Examiner asserts that Kawamoto *et al.* taught *in vivo* transplantation of endothelial progenitor cells obtained from mononuclear cells, and isolated tissue comprising endothelial cells that had transdifferentiated from said mononuclear cells *in vivo*. Applicants respectfully traverse this rejection.

It appears the Examiner has mistakenly applied Kume *et al.*, Pufe *et al.*, and Howett *et al.* to claim 12 because claim 12 is only dependent on claim 1. Clarification from the Examiner is requested. Regardless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, and Howett *et al.* does not render obvious the use of a retrovirus expressing PTN to induce differentiation of the monocytic cells into endothelial cells as discussed in detail above. Thus, the combination including Kawamoto *et al.* does not render it obvious to first transduce a retrovirus expressing PTN into the monocytic cell to induce differentiation into an endothelial cells and then allow the differentiation to occur *in vivo*. In light of the above, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claims 5 and 13 stand and claims 15 and 18 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* for reasons of record. Applicants respectfully traverse this rejection.

As discussed above, the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* does not render obvious a method of transdifferentiating a monocytic cell into an endothelial cell by transducing the monocytic cell with a retrovirus expressing PTN. Accordingly, for the same reasons, Havemann *et al.*, Souttou *et al.* and Powers *et al.* does not render obvious an isolated

endothelial cell produced by the same method. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 7 stands and claim 16 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.*, as applied to claims 5, 13, 15, and 18 *supra*, and in further view of Kume *et al.* for reasons of record. Applicants respectfully traverse this rejection.

Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.* and Kume *et al.* would not render claim 7 or claim 16 obvious. As discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 5, 13 or 15 obvious because the combination does not render obvious a method of transdifferentiating a monocytic cell into an endothelial cell by transducing the monocytic cell with a retrovirus expressing PTN, and therefore would not render obvious an isolated endothelial cell produced by the same method. Since claims 7 and 16 depend from claims 5 and 15, respectively, all the aforementioned reasons apply and it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell, and the same reasonable expectation of success. Since there is no predictability and no reasonable expectation of success from the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.*, there will not be any predictability or reasonable expectation of success for the combination of Havemann *et al.* Souttou *et al.*, Powers *et al.* and Kume *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 8 stands and claim 17 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, and Kume *et al.* as applied to claims 5, 7, 13, 15-16, and 18 *supra*, and in further view of Pufe *et al.*, Howett *et al.*, and Eslami *et al.* for reasons of record. Applicants respectfully traverse this rejection.

Applicants again suspect and submit that Kume *et al.* was erroneously applied to the rejection of claim 8. The Examiner has applied Kume *et al.* to reject claim 7; however, claim 8

does not depend from claim 7. As such, Kume *et al.* does not appear to be applicable to claim 8. Applicants again request clarification regarding Kume *et al.* Nonetheless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* would not render claim 8 obvious. As discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 5 obvious, because, among other things, there would not be any reasonable expectation of success. Since claim 8 depends from claim 5, it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same reasonable expectation of success. Since there is no predictability and no reasonable expectation of success from the combination of Havemann *et al.*, Souttou *et al.*, and Powers *et al.*, there will not be any predictability or reasonable expectation of success for the combination of Havemann *et al.* Souttou *et al.* Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.*, and Eslami *et al.*, as applied claims 5, 7-8, 13, and 15-18 *supra*, and in further view of Kawamoto *et al.* for reasons of record. Particularly, the Examiner implies that Havemann *et al.* discloses that genetically modified monocytes transdifferentiate the monocytes into endothelial cells. Applicants respectfully traverse this rejection.

Contrary to the Examiner's statements, Havemann *et al.* does not make any disclosures that genetically modified monocytes transdifferentiate into endothelial cells. Thus, the Examiner's reasoning that one of ordinary skill in the art would have substituted the *in vitro* transdifferentiation step with an *in vivo* transdifferentiation step, based on this erroneous assumption, is flawed. The Examiner appears to equate proliferation of endothelial cells with transdifferentiation properties. This is simply incorrect. Pufe *et al.*'s teaching regarding the ability of PTN to enhance proliferation of endothelial cells does not equate to PTN's ability to

induce transdifferentiation of monocytes into endothelial cells. None of the references cited by the Examiner teaches the use of PTN to transdifferentiate monocytes into endothelial cells.

Applicants submit that the combination of Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, and Howett *et al.* does not teach the use of a retrovirus expressing PTN to induce differentiation of the monocytic cells into endothelial cells as discussed in detail above. Thus, the combination including Kawamoto *et al.* does not render it obvious to first transduce a retrovirus expressing PTN into the monocytic cell to induce differentiation into an endothelial cell and then allow the differentiation to occur *in vivo*. In light of the above, Applicants respectfully request reconsideration and withdrawal of this rejection.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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